A Targeted Literature Review of Treatment Sequencing Approaches in Economic Analyses in Relapsing Multiple Sclerosis

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Objective

To understand the methods and data assumptions used in treatment sequencing in economic evaluations, reviewing published economic evaluations in relapsing multiple sclerosis (RMS) as a case study.

Background

- Treatment pathways are constantly evolving, with newly-developed therapies providing patients with an ever-increasing number of treatment options.
- To more accurately represent the patient experience, treatment sequencing can be included in an economic evaluation, thereby increasing the complexity of the model.
- Due to the continual and often concurrent development of treatments, there is little evidence to support the efficacy of different treatments when used in sequence. Furthermore, there is often a lack of consensus on preferred treatment sequences in practice, given each patient experience is unique.

Methods

- RMS is a chronic condition that requires ongoing treatment and has a crowded treatment pathway. English and European guidelines recommend that multiple treatments are cycled through when treating RMS.[1,2] This research therefore used RMS as a case study to assess the extent to which economic evaluations consider treatment sequencing, when treatment sequencing occurs in clinical practice.
- A targeted literature review (TLR) was conducted to explore treatment sequencing in RMS, as an update to a previous systematic literature review (SLR) of economic evaluations in RMS.[3] In line with the previous SLR, MEDLINE, Embase, and EBM Reviews databases were searched using the same search terms and restrictions.
- In the original SLR, databases were searched from database inception to 15 February 2021. Some studies published in 2019 were missed in the original SLR and so the updated TLR searches were run from 1 January 2019 to 8 May 2023.
- Studies were included if they were freely available published cost-effectiveness, cost-utility, or cost-benefit models. Health technology assessment (HTA) submissions were excluded, given prior research has focussed on the inclusion of treatment sequencing in HTA submissions.[4]
- Only studies from 2018 onwards, in English, were included. As the more recent treatment pathway includes a large number of potential treatments for RMS, results published after 2018 are more relevant when analysing treatment sequence modelling.
- Data extraction was performed using Microsoft Excel. The approach to the review is presented in **Figure 1**.

Results

- Of the 447 abstracts initially identified during the updated searches, 40 publications were included in the final review. Combined with the original SLR results, 73 unique studies were included. The publications mostly reported on Markov models (n=57), however other analyses included microsimulations (n=5), trial-based analysis (n=1), or a combination (n=1). A model type was not reported in eight studies and one study was a retrospective chart review without a model.
- Treatment sequencing was reported in 14 (19.2%) publications, as presented in **Figure 2** and **Figure 3**.
- The number of different sequences in a given model ranged from 2 to 445, with most models including two (n=7, 50.0%) (**Figure 2**). Similarly, most models included two treatments in sequence (n=8, 57.1%) and the longest sequence comprised up to nine treatments (n=1) (**Figure 3**).
- Analyses were split into those that directly compared different specific sequences (n=10), and those that optimised between all possible treatments to identify the ideal sequence (n=4).
- The most observed sequencing pattern involved patients commencing treatment on an immunomodulator (n=8), with most studies investigating sequencing to a monoclonal antibody (n=4). Other treatments modelled subsequent to an initial immunomodulator included: another immunomodulator (n=2), a sphingosine-1-phosphate receptor modulator (n=2), or a generic disease modifying therapy (n=2).
- Beyond the first subsequent treatment, there was no particular pattern in any sequence. This could be due to the fact that since UK and European treatment guidelines were published in 2018, multiple new treatments have been licensed in this indication and so later lines of therapy are constantly evolving. The lack of pattern could also be due to the fact that the studies spanned across seven countries in Europe and South America.
- Of the publications that reported the data informing treatment effectiveness in the sequence (n=6), subsequent treatment effectiveness was either directly observed (n=2) or assumed to not depend on timing or place in the treatment sequence (n=4).

Conclusions

Despite the numerous RMS treatments available, treatment sequence modelling remains limited and there is no universal method for modelling treatment effectiveness at later lines. Most often, a simple assumption is made in which equal efficacy is assumed regardless of treatment line. As a result, the patient experience and recommended treatment pathways in clinical guidelines are not consistently represented in RMS economic evaluations, which limits the relevance of analyses for informing decision-making.

Published economic evaluations in RMS should more routinely provide justification if treatment sequencing is not modelled; modelling sequencing in scenarios would help to address the impact of this modelling choice.

FIGURE 1

PRISMA diagram presenting the number of studies at each stage of the review

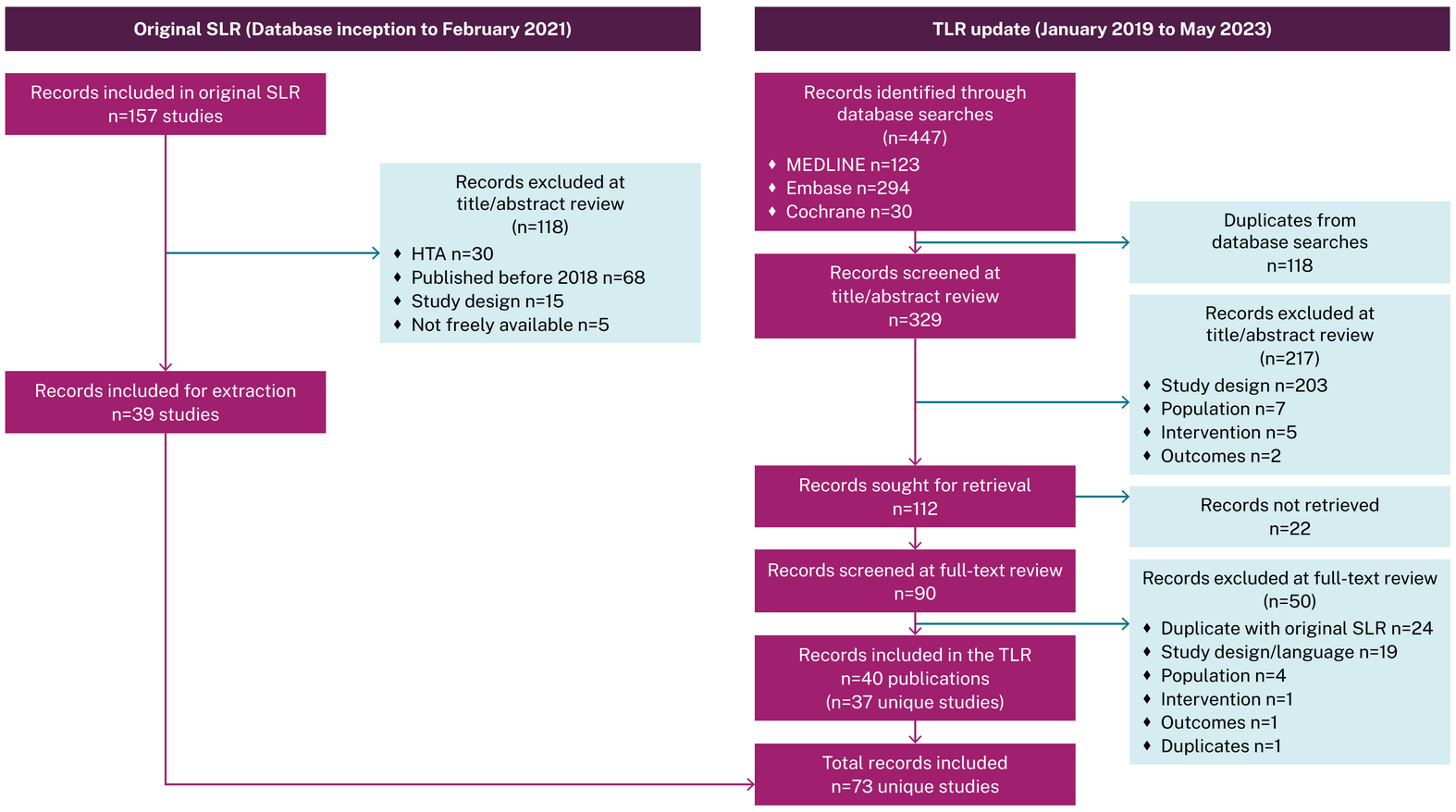
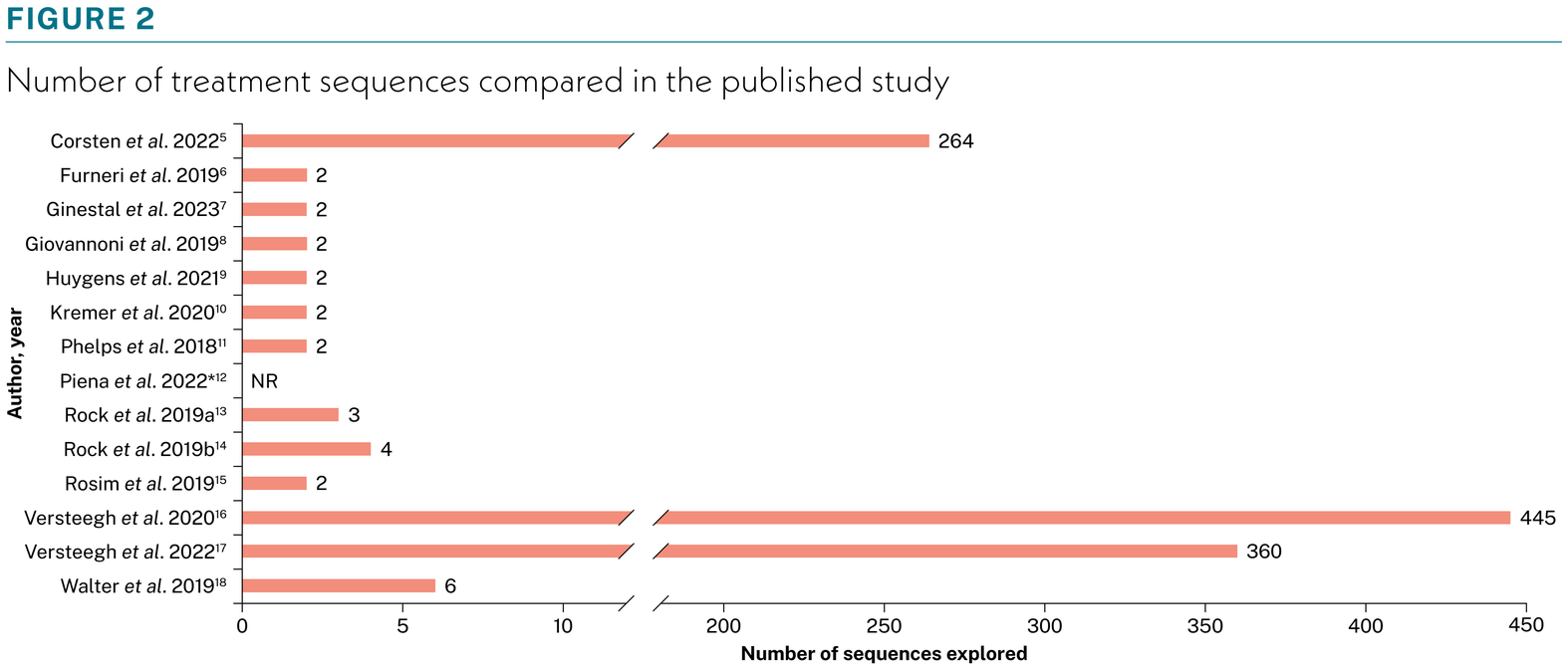


FIGURE 2

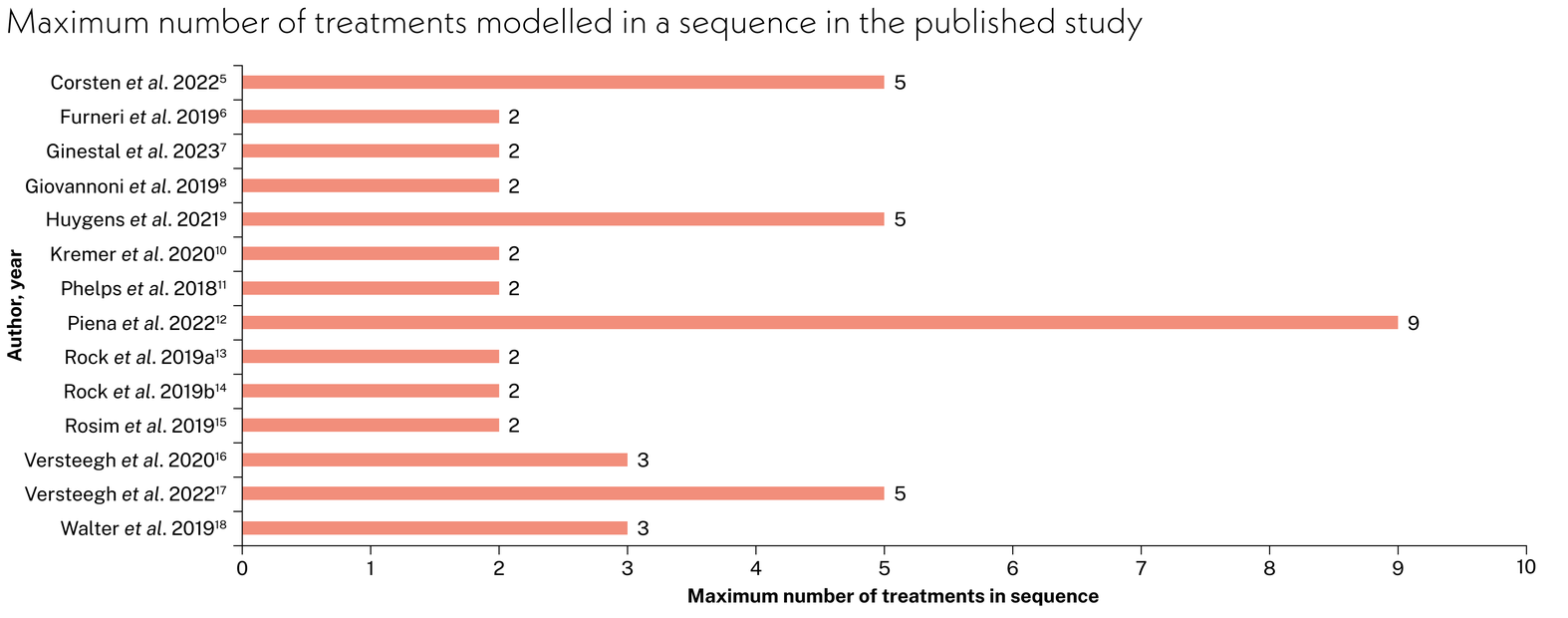
Number of treatment sequences compared in the published study



*Piena *et al*. 2022 did not report a specific number of sequences being compared, however allowed any combination of up to 9 disease modifying treatments in their analysis.

FIGURE 3

Maximum number of treatments modelled in a sequence in the published study



Abbreviations: HTA: health technology assessment; **NR:** not reported; **PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **RMS:** relapsing multiple sclerosis; **SLR:** systematic literature review; **TLR:** targeted literature review.

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